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CORPORATE SOURCE: Department of Radiotherapy, University Hospital of Ostrava, Ostrava-Poruba, Czeck Republic.. pavlina.plevova@fnspo.cz
SOURCE: ORAL ONCOLOGY, (1999 Sep) 35 (5) 453-70. Ref: 225
Journal code: 9709118. ISSN: 1368-8375.
PUB. COUNTRY: ENGLAND: United Kingdom
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2. ACCESSION NUMBER: 95211031 MEDLINE
DOCUMENT NUMBER: 95211031 PubMed ID: 7696971
TITLE: IL-11, a pleiotropic cytokine: exciting new effects of IL-11 on gastrointestinal mucosal biology.
AUTHOR: Keith J C Jr; Albert L; Sonis S T; Pfeiffer C J; Schaub R G
CORPORATE SOURCE: Genetics Institute, Inc., Cambridge, Massachusetts.
SOURCE: STEM CELLS, (1994) 12 Suppl 1 79-89; discussion 89-90.
Journal code: 9304532. ISSN: 1066-5099.
PUB. COUNTRY: United States

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3. ACCESSION NUMBER: 2000453978 MEDLINE
DOCUMENT NUMBER: 20464824 PubMed ID: 11012229
TITLE: The clinical development of recombinant human interleukin 11 (NEUMEGA rhIL-11 growth factor).
AUTHOR: Kaye J A
CORPORATE SOURCE: Clinical Research/Hematology, Genetics Institute, Inc., Cambridge, Massachusetts 02140, USA.
SOURCE: STEM CELLS, (1996) 14 Suppl 1 256-60. Ref: 26
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4. DOCUMENT NUMBER: 97392673 PubMed ID: 9245489
TITLE: Mitigating effects of interleukin 11 on consecutive courses of 5-fluorouracil-induced ulcerative mucositis in hamsters.
AUTHOR: Sonis S T; Van Vugt A G; McDonald J; Dotoli E; Schwertschlag U; Szklut P; Keith J
CORPORATE SOURCE: Division of Oral Medicine Oral and Maxillofacial Surgery, and Dentistry, Brigham & Women's Hospital, Boston, MA 02115, USA.
SOURCE: CYTOKINE, (1997 Aug) 9 (8) 605-12.

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The Clinical Development of Recombinant Human Interleukin 11 (NEUMEGA™ rhIL-11 Growth Factor)

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Key Words. Recombinant human interleukin 11 (rhIL-11) • Interleukin 11 (IL-11) • Cytokine • Megakaryocytopoiesis • Neoplasms • Chemotherapy • Thrombocytopenia • Mucositis

Abstract. Completed phase I and II studies of recombinant human interleukin 11 (rhIL-11) demonstrate its potential as a treatment for chemotherapy-induced thrombocytopenia.

In a phase I study, 16 women with breast cancer received rhIL-11 (10, 25, 50, 75 or 100 μg/kg s.c. once daily) before and during cycles of moderately dose-intensive chemotherapy. Platelet counts increased in all patients before chemotherapy. During chemotherapy, the mean platelet count nadirs were 67,000 cells/μl (rhIL-11 10 μg/kg) and greater than 150,000 cells/μl (25, 50 and 75 μg/kg). Thus, doses of 25 μg/kg and higher appeared to prevent chemotherapy-induced thrombocytopenia in this study.

In a randomized, placebo-controlled study, rhIL-11 (50 μg/kg) prevented the need for platelet transfusions during a subsequent chemotherapy cycle in patients who had already experienced severe chemotherapy-induced thrombocytopenia. Among 82 evaluable patients, 8 (30%) of 27 patients administered rhIL-11 50 μg/kg avoided platelet transfusions versus one (4%) of 28 who received placebo ($p < 0.05$). rhIL-11-treated patients received approximately two-thirds the number of platelet transfusions that placebo-treated patients received. The median duration of thrombocytopenia (<50,000 cells/μl) was seven days in rhIL-11-treated patients compared to 10 days among patients given placebo.

This is the first study in which patients with a history of severe chemotherapy-induced thrombocytopenia who were receiving a variety of chemotherapy regimens have been shown to avoid platelet transfusions following the administration of a thrombopoietic growth factor. This activity of rhIL-11, and the demonstration in preclinical models that it ameliorates chemotherapy-induced mucositis, have promoted its further clinical development as a supportive therapy in patients receiving chemotherapy.
Stem Cells 1996;14(suppl 1):256-260

Introduction

Interleukin 11 (IL-11) has been shown to be an important multifunctional thrombopoietic growth factor in both in vitro and in vivo investigations. In vitro, IL-11 enhances the growth of early hematopoietic stem cells [1-7] and stimulates megakaryocytopoiesis synergistically with other hematopoietic growth factors such as IL-3 [8-11]. In vivo, IL-11 increases platelet production in a variety of both normal and myelosuppressed animal models [12-17].

Recombinant human (rh)IL-11 (NEUMEGA™ rhIL-11 Growth Factor) is under clinical development for the treatment of thrombocytopenia, a frequent dose-limiting side effect of chemotherapy. The elimination or decreased need for platelet transfusions in thrombocytopenic patients is the therapeutic goal of the clinical studies. Results from a phase II randomized, placebo-controlled, multicenter study (described below) demonstrated the ability of rhIL-11 to prevent the need for platelet transfusions.

Clinical Studies of rhIL-11

Several clinical studies of rhIL-11 in patients with thrombocytopenia have been completed or are nearing completion. Breast cancer patients with moderate thrombocytopenia (i.e., not requiring platelet transfusions) were studied first. In subsequent studies, rhIL-11 has been evaluated in

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patients with more severe thrombocytopenia to assess its ability to prevent or reduce the need for platelet transfusions.

In a phase I study, rhIL-11 was given to women with stage IIIB and IV breast cancer before and during cycles of moderately dose-intensive chemotherapy with cyclophosphamide (1500 mg/m^2) and doxorubicin (60 mg/m^2) [18]. Patients whose chemotherapy could be delayed for one month were selected so they could receive a 14-day course of rhIL-11 treatment followed by a 14-day rest period before beginning their chemotherapy. During the pre-chemotherapy cycle, cohorts of at least three patients were treated with rhIL-11 administered s.c. once daily at doses of 10, 25, 50 or 75 μg/kg; one additional patient was treated with a dose of 100 μg/kg. Beginning one day after chemotherapy, the cohorts were treated with rhIL-11 s.c. once daily at doses of 10, 25, 50 or 75 μg/kg for 12 days.

During the pre-chemotherapy cycle of rhIL-11 treatment, adverse events consisted mainly of mild or moderate constitutional complaints, primarily fatigue, headache, and arthralgias or myalgias. Only fatigue was reported commonly. Blood hemoglobin concentrations decreased in all patients during rhIL-11 treatment; the concentrations returned to normal levels during the two weeks after treatment. No bleeding or hemolysis was evident, and direct measurement of red blood cell mass and plasma volume in a few patients suggested that the hemoglobin decreases were due to increases in plasma volume (dilutional anemia). This mechanism for the anemia associated with rhIL-11 administration subsequently was confirmed in a study involving normal volunteer subjects [19]. Less frequent adverse events were nasal or sinus stuffiness, nausea, injection-site redness or swelling, edema and tachycardia. With the exception of myalgia and arthralgia, there was little evidence that any of these adverse events, including the dilutional anemia, were dose-related within the dose range tested. rhIL-11 did not cause any clinically significant fevers.

During the pre-chemotherapy cycle, increases in platelet counts were observed in all patients treated with rhIL-11 at doses of 10 to 75 μg/kg. The increase in platelet counts appeared to be dose-related. The maximum increase was approximately fourfold above the pretreatment level. During the chemotherapy cycle, the mean platelet count nadir in patients receiving rhIL-11 at a daily dose of 10 μg/kg was 67,000 cells/μl, approximately the same decrease as that expected from the myelosuppressive effect in patients receiving the same chemotherapy without an hematopoietic growth factor. In contrast, mean platelet count nadirs in the groups receiving rhIL-11 at doses of 25, 50 and 75 μg/kg were all greater than 150,000 cells/μl. During a second cycle of treatment, the mean platelet count nadir in the 10-μg/kg group was 44,000 cells/μl, whereas the mean nadirs in the 25-, 50-, and 75-μg/kg groups were all greater than 100,000 cells/μl. Platelet aggregometry testing showed no treatment-related abnormality of platelet function.

In this phase I study, concomitant administration of G-CSF was permitted after the second chemotherapy cycle in any patient who had already experienced an episode of neutropenic fever. The average duration of severe neutropenia (ANC < 500 cells/μl) was 6.6 days during cycles in which no myeloid growth factor was administered. The average duration of severe neutropenia was 2.6 days during chemotherapy cycles that included concomitant rhIL-11 and G-CSF treatment. Thus, rhIL-11 did not appear to prevent G-CSF from shortening the period of severe neutropenia after chemotherapy.

A randomized, placebo-controlled, double-masked, multicenter phase II study examined the ability of rhIL-11 (25 and 50 μg/kg) to prevent the need for platelet transfusions in patients with solid tumors or lymphoma. Before entering the study, the patients had already experienced severe chemotherapy-induced thrombocytopenia (platelet count nadir ≤20,000 cells/μl) and had required at least one platelet transfusion during the preceding cycle of chemotherapy [20]. The patients had been receiving a variety of chemotherapy regimens, including ICE (ifosfamide, carboplatin and etoposide), DICEP (cyclophosphamide, etoposide and cisplatin), MAID (mesna, doxorubicin, ifosfamide and dacarbazine), DHAP (dexamethasone, cytarabine and cisplatin) and others. The regimens (agents, doses and schedule) administered during the study were the same as those given during the previous chemotherapy cycle. To assess the severity of thrombocytopenia at the nadir, blood counts were measured at least three times weekly, and daily counts were required if the most recent platelet count was <50,000 cells/μl. In accordance with the most commonly followed oncology practice [21], platelets were

transfused prophylactically for platelet count nadirs of ≤20,000 cells/μl.

Eighty-two patients were evaluable for the primary efficacy endpoint, which was the elimination of prophylactic platelet transfusions during the cycle of chemotherapy administered with masked study drug. Eight (30%) of 27 evaluable patients who received 50 μg/kg of rhIL-11 did not require any platelet transfusions during the study cycle compared to 1 (4%) of 27 patients in the placebo group ($p < 0.05$). The response rate in the 25-μg/kg group was 5 (18%) of 28 patients, suggesting a benefit; the rate, however, was not statistically different from that of the placebo group ($p = 0.23$). Investigators and patients complied with the blood count monitoring and platelet transfusion policies without apparent bias.

Analysis of a secondary endpoint showed that patients treated with rhIL-11 received approximately two-thirds the number of platelet transfusions received by patients treated with placebo. The median duration of thrombocytopenia (<50,000 cells/μl) was seven days in patients treated with rhIL-11 compared to 10 days among the placebo-treated patients.

rhIL-11 generally was well-tolerated in the phase II study. Patients administered rhIL-11 experienced cardiovascular adverse events, including a low incidence of uncomplicated atrial arrhythmia or syncope, more frequently than placebo-treated patients. Risk factors for atrial arrhythmias were older age and a history of atrial arrhythmia during a previous chemotherapy cycle. An increase in plasma volume stimulated by rhIL-11 treatment is postulated to cause such events in susceptible patients [19]. This plasma volume increase can be reduced substantially with an oral diuretic, according to results from a recent normal volunteer study [unpublished results].

Further Clinical Investigations

Results from completed clinical studies of rhIL-11 demonstrate its potential use in cancer treatment. The ability of rhIL-11 to prevent the need for platelet transfusions has been demonstrated in a phase II study of patients with a variety of cancers who were administered an array of chemotherapy regimens. Additional phase II trials are ongoing, and a multicenter phase III study is underway to confirm these findings. Another phase II, double-masked, randomized, placebo-controlled study is evaluating rhIL-11 in patients with breast cancer receiving high-dose cyclophosphamide and doxorubicin, who are likely to develop severe thrombocytopenia as a result of their chemotherapy and require platelet transfusions. Other ongoing studies include a randomized, placebo-controlled phase II study in patients receiving extremely high-dose chemotherapy followed by autologous bone marrow transplantation with peripheral blood stem cell support and a phase I study in pediatric oncology patients.

rhIL-11 may provide clinical benefits in addition to its ability to stimulate platelet production. For example, the plasma concentrations of both fibrinogen and von Willebrand factor increase after treatment with rhIL-11 [22]. Fibrinogen plays important roles in coagulation, platelet aggregation and wound healing, while von Willebrand factor is critical for platelet adhesion to the subendothelium at sites of vascular injury. The broader physiologic role of rhIL-11 in response to hemostatic stress may prove important in the potential use of rhIL-11 as a treatment for conditions other than chemotherapy-induced thrombocytopenia.

Like thrombocytopenia, mucositis often limits the dose intensity of chemotherapy. Preclinical studies have demonstrated the beneficial effect of rhIL-11 in a variety of animal models of gastrointestinal epithelial injury. In hamsters, rhIL-11 ameliorated oral mucositis induced by treatment with 5-fluorouracil and subsequent irritation of cheek-pouch mucosa, a technique used to mimic the development of similar lesions in patients with cancer [23]. In mice receiving total body irradiation, rhIL-11 treatment has been shown to improve the survival of clonogenic cells in small intestinal crypts [24]. These effects may be mediated directly through the ability of rhIL-11 to inhibit the proliferation of small intestinal epithelial cells [25], or indirectly through its ability to downregulate the production of inflammatory mediators such as tumor necrosis factor [26] (or by both direct and indirect mechanisms).

rhIL-11 is under investigation in patients receiving a high-dose chemotherapy regimen with autologous hematopoietic stem cell support who have a high incidence of both chemotherapy-induced thrombocytopenia and mucositis. These studies soon will provide important additional information about the utility of rhIL-11 in oncology practice.

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